Environmental Health Perspectives
Vol. 96, pp. 11-15, 1991

The Carcinogenic Potency Database: Analyses of 4000 Chronic Animal Cancer Experiments Published in the General Literature and by the U.S. National Cancer Institute/National Toxicology Program

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The Carcinogenic Potency Database (CPDB) is an easily accessible, standardized resource of positive and negative long-term animal cancer tests. The CPDB has been published in four earlier papers that include results for approximately 4000 experiments on 1050 chemicals. This paper describes the CPDB: goals, inclusion criteria, fields of information, and published plot format. It also presents an overview of our published papers using the CPDB. The CPDB as published in plot format readily permits comparisons of carcinogenic potency and many other aspects of cancer tests, including for each experiment the species and strain of test animal, the route and duration of compound administration, dose level and other aspects of experimental protocol, histopathology and tumor incidence, TD_{50} (carcinogenic potency) and its statistical significance, dose response, author's opinion about carcinogenicity, and literature citation. A combined plot of all results from the four separate papers, which is ordered alphabetically by chemical, is available from L. S. Gold, in printed form or on computer tape or diskette. A computer readable (SAS) database is also available.

The overview of papers includes descriptions of work on methods of estimating carcinogenic potency, reproducibility of results in near-replicate cancer tests, correlation in potency between species, ranking possible carcinogenic hazards, comparison of positivity and target organ in rats and mice, comparison of mutagens and nonmutagens, proportion of chemicals positive in animal tests, natural compared to synthetic chemicals, and mechanistic issues in interspecies extrapolation.

Description of the Carcinogenic Potency Database

Background

Development of the Carcinogenic Potency Database (CPDB) began more than a decade ago. Experimental protocols of chronic animal cancer tests as well as the type of information reported by scientists in the literature are quite diverse, and the large body of published results was not easily accessible. Our goals in developing the CPDB included: *a*) to provide a standardized resource of positive and negative long-term tests so that results could be compared; *b*) to provide estimates of a single index of carcinogenic potency for a large number of substances so that rodent potency could be compared to other factors such as mutagenicity, teratogenicity, chemical structure, and human exposure; *c*) to provide easy access to results in printed form; *d*) to report detailed information on each experiment including qualitative information on strain, sex, target organ, histopathology and author's opinion, as well as quantitative information on statistical significance, tumor incidence, dose–response curve shape, length of experiment, dose rate, and duration of dosing; and *e*) to use the database to investigate important issues such as reproducibility of results, correlations in carcinogenic potency, proportions of chemicals that are carcinogenic, and prediction of positivity and target organ between species.

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The CPDB has been published in four papers in plot format (*1–4*) and is a widely used, standardized resource of results on approximately 4000 experiments of 1050 chemicals that were reported either in the general literature or in technical reports of the National Cancer Institute/National Toxicology Program (NCI/NTP). We are continuing to update the CPDB and have also prepared a combined plot that merges all earlier results organized by chemical; the combined plot can be obtained from L. S. Gold in either printed form, on diskette, or tape. A computer readable (SAS) database is also available.

Inclusion Rules

Our standard inclusion criteria are designed to identify for the CPDB reasonably thorough, chronic long-term tests that permit the estimation of carcinogenic potency; therefore, reasonable consistency of experimental protocols is assured. Bioassays are included only if they meet the criteria listed in Table 1.

The TD_{50}

The TD_{50} is our numerical index of potency and has been fully described (*1,5,6*). The TD_{50} may be briefly defined as follows: for a given target site(s), if there are no tumors in control animals, then TD_{50} is that chronic dose rate in milligrams/kilogram body weight/day that would induce tumors in half the test animals at the end of a standard lifespan for the species. Since the tumor(s) of interest often does occur in control animals, TD_{50} is more precisely defined as that chronic dose rate that will halve the probability of remaining tumor-free throughout the standard lifespan. One reason for choosing the TD_{50} was that it is easy to understand the concept, particularly because of the analogy to the LD_{50}. Importantly, the TD_{50} is often within the range of doses tested; thus the experimental results do not have to be extrapolated far to estimate TD_{50}. The range of statistically significant TD_{50} values for carcinogens in the CPDB is more than 10 millionfold (*1*).

Plot Format and Features

A detailed guide to the plot of the CPDB was included in Gold et al. (*1*); it described the contents, field by field, and discussed sources of data, criteria for inclusion of particular target sites, and conventions adopted in summarizing the literature. For each experiment in the CPDB, a TD_{50} is reported whenever documentation in the original paper is adequate for: *a*) each target site evaluated by the author as treatment related; *b*) each site with a statistically significant result; *c*) all tumor-bearing animals; *d*) data on liver and also on lung for mice. Items *c* and *d* are "mandatory sites." Appendices following the plot facilitate identification of chemicals by name, synonyms, and CAS number; they also define codes for strains, routes of administration, sites, histopathology, author's opinions, dose–response curve symbols; and literature references. A sample of the plot and description for one experiment is given in Figure 1.

Table 1. Criteria for inclusion in the Carcinogenic Potency Database.

Animals on test were mammals
Administration was begun early in life
Route of administration was diet, water, gavage, inhalation, intravenous or intraperitoneal injection (i.e., where the whole body was more likely to have been exposed rather than only a specific site, as with subcutaneous injection or skin painting)
Test agent was administered alone, rather than in combination with other chemicals
Exposure was chronic, with less than 8 days between doses
Duration of exposure was at least one-fourth the standard lifespan for that species
Duration of experiment was at least half the standard lifespan for that species
Research design included a control group
Research design included at least five animals per group
Surgical intervention was not performed
Author reported number of animals with tumor, not number of tumors
Results reported were original data, not secondary analyses

A unique number is assigned to each experiment in the CPDB plot, and lowercase letters for subsequent lines identify each TD_{50} calculated for that experiment. The number inserted above each field in Figure 1 corresponds to the description below. [1] Chloroform is the chemical; [2] R: species is rat; [3] m: sex is male; [4] osm: strain is Osborne-Mendel; [5] gav: route of administration is gavage; [6] kid: site is kidney; [7] MXA: histopathology is a mix of tumor types combined by NCI. The pathology is indicated on the right side of the plot under [27] where the codes are "kid:tla, uac," indicating a mix of tubular-cell adenoma and tubular-cell adenocarcinoma. The site and histopathology is reported in the nomenclature used in the original published paper or technical report. [8] 18m: length of exposure is 18 months; [9] 26m: length of experiment is 26 months. [10] "Notes" is blank here but is used to describe particulars such as survival problems or variable dosing schedules. [11] Logarithmic scale for TD_{50} and confidence limits. [12] The plotted TD_{50} value with the symbol "+" indicating that the statistical significance of the TD_{50} is $p < 0.01$. The colon indicates the 99% confidence limits for TD_{50} and shows that TD_{50} was calculated with lifetable data; [13] 119.mg: value of TD_{50} in milligrams/kilogram/day. [14] Shape of the dose–response curve, determined by a test for departure from linearity. The solidus (/) indicates significant departure from linearity with upward curvature. [15] $p < 0.0005$: two-tailed p-value associated with testing whether the slope of the dose–response curve is different from zero. [16] c: NCI opinion that chloroform was carcinogenic, inducing the tumors indicated under [6] and [7]. The right side of the plot repeats as [17] the experiment number. [18] 67-66-3: CAS registry number for chloroform; [19] c02686: unique reference number for a paper or an NCI/NTP identification number; [20–21] 65.5mg and 334.mg: lower and upper confidence limits for the TD_{50} in milligrams/kilogram/day. [22–26] Proportion of animals with tumors in [6–7] and average daily dose rate in milligrams/kilogram/day for the control group and each dose group. For NCI/NTP the denominator indicates the starting number of animals, and the numerator indicates the number of animals with tumors by the end of the experiment. [27] Codes for histopathology for NCI/NTP and literature citation for papers published in the general literature. Lines a and b under this experiment give results for mandatory sites that are always included in the database whenever data are available. TBA: all tumor-bearing animals; and liv: liver. Futher details on the plot are given in Gold et al. (*1*).

To facilitate access to bioassay results for researchers interested in a particular target tissue (e.g., for studies of mechanism, comparative toxicology and histopathology, or epidemiology), we recently prepared a compendium organized by target organ for

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     Spe Strain  Site    Xpo+Xpt                                                                    TD50     2Tailpvl
       Sex   Route   Hist      Notes                                                                    DR     AuOp
[1] [2][3][4][5] [6] [7] [8][9][10]                          [11]              [12]                  [13] [14][15][16]

CHLOROFORM***                    100ng..:..1ug....:..10.....:..100....:..1mg....:..10.....:..100....:..1g.....:..10
 1   R m osm gav kid MXA 18m26                                                  : +    :              119.mg / P<.0005c
 a   R m osm gav TBA MXB 18m26                                                                        194.mg * P<.5
 b   R m osm gav liv MXB 18m26                                                                       455.mg * P<.08

Left side of database plot.


     RefNum  LoConf UpConf   Cntrl  1Dose    1Inc  2Dose    2Inc                    Citation or Pathology
                                                                                                  Brkly Code
[17][18][19] [20]   [21]     [22]   [23]    [24]   [25]    [26]                                  [27]

CHLOROFORM***   67-66-3
 1   c02686  65.5mg 334.mg   0/20   45.2mg   4/50  90.3mg  12/50                                    kid:tla,uac.
 a   c02686  43.5mg n.s.s.   9/20   45.2mg  24/50  90.3mg  20/50
 b   c02686  157.mg n.s.s.   0/20   45.2mg   1/50  90.3mg   3/50                                  liv:hpa,hpc,nnd.

Right side of database plot.
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FIGURE 1. Sample plot for one experiment in the Carcinogenic Potency Database.

522 chemicals that are carcinogenic in at least one species. The compendium can be used to identify quickly all chemicals that induce tumors at a particular site and to determine whether target sites are the same for chemicals positive in more than one species. Chemical carcinogens are reported for 35 different target organs. Overall, 94% of mouse carcinogens and 83% of rat carcinogens are positive in at least one of the eight most frequent target sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system, and urinary bladder (*7*).

Some general characteristics of the CPDB are as follows: Among the 1050 chemicals, 427 have been tested in both rats and mice, and 270 have been tested by NCI/NTP. Tests are also included on hamsters, dogs, and monkeys. Results are included on 96 different mouse strains and 72 rat strains. In the CPDB the number of experiments per chemical varies, and some chemicals are more thoroughly tested than others. The percentages with one experiment, two experiments, and more than two experiments are 30, 52, and 18%, respectively, for rats and 12, 56, and 32%, respectively, for mice.

Overview of Our Published Papers Using the Carcinogenic Potency Database

We have used the CPDB to address many issues relevant to carcinogenesis and interspecies extrapolation. We summarize this work below and refer the reader to the published papers.

With respect to the measurement of carcinogenic potency, we first compared two methods for estimating TD_{50} from animal bioassays, one based on lifetable data and one based on summary incidence data (*8*). There is substantial agreeement between these methods, although lifetable estimates are usually more potent. This similarity provides confidence in TD_{50} estimates based only on summary data, which are all that are usually available in the literature. Second, we have shown that the potency calculated from experimental results (given the usual experimental design and the lack of 100% tumor incidence in dosed animals) is restricted to an approximately 30-fold range surrounding the maximum dose tested in a standard bioassay (*9*). Third, for chemicals that are positive in more than one test in a species, the most potent TD_{50} value from among all positive tests is smiliar to other measures that average TD_{50} values or functions of values (harmonic mean, geometric mean, or arithmetic mean). However, for 18 chemicals in rats and 12 in mice, the minimum TD_{50} estimate differs from the maximum estimate by more than a factor of 10; for these relatively few carcinogens, any summary measure of potency masks the variation across experiments (*10*). Using the most potent TD_{50} in rats and mice, we have published a concise tabulation of the TD_{50} for positive chemicals, which also includes a summary of the evaluations as to carcinogenicity in each sex–species group (*10*).

Correlation studies of carcinogenic potency have been conducted. We have discussed some tautologous aspects of the good correlation in potency between rats and mice (*9*) and have reported a weak association of mutagenic potency and carcinogenic potency for 80 chemicals that are both mutagenic in Salmonella and carcinogenic in rats or mice (*11*).

A single measure of potency like TD_{50} can summarize only some of the information from a carcinogenesis bioassay. We have investigated other indicators of a chemical's hazard using the NCI/NTP bioassays, i.e., whether tumors were induced at more than one site, whether tumors may have caused the death of the animal or were found at sacrifice, and whether metastases of induced tumors occurred (*12*). These hazard indicators are sometimes interrelated; however, the TD_{50} values of chemicals that are hazardous by each of these measures span a wide range. Carcinogens that induced some type of fatal tumor were more likely than other carcinogens to induce tumors in multiple organ sites and multiple sex–species groups. These other indicators should be used with potency estimates to summarize and compare results on chemical carcinogens.

Reproducibility of results in animal bioassays has been investigated in near-replicate comparisons consisting of two or more tests of the same chemical administered by the same route using the same sex and strain of rodent (*13*). We have updated this analysis and continue to find that overall in the CPDB there is

good reproducibility of positivity, target site, and TD_{50}. Among 116 comparisons only 14% (16/116) have discordant author's opinions about whether tumors were induced in the individual experiments. In all but 3 of the 62 positive comparisons, at least 1 target site is identical in all of the near-replicate tests. The TD_{50} values were within a factor of 2 of each other in 54% of the positive comparisons, within a factor of 4 in 81%, and within a factor of 10 in 91%.

We have proposed a rough index of possible carcinogenic hazard to humans, HERP (human exposure/rodent potency), which compares for a given chemical the chronic dose rate at which humans are exposed (milligrams/kilogram/day) to the TD_{50} in rodents. We have computed HERP values for a variety of synthetic and naturally occurring substances to which people may be exposed and have constructed a scale to rank possible hazards. This ranking suggests that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances, though one cannot say whether these natural exposures are likely to be of major or minor importance in human cancer (*14–20*). In a separate analysis, a similar index, PERP (permitted exposure/rodent potency) was calculated using the U.S. Occupational Safety and Health Administration permitted exposure limit (OSHA PEL), assuming a daily lifetime exposure at that limit. From among approximately 500 compounds in the CPDB that are rodent carcinogens and approximately 500 that are regulated with PELs by OSHA, only 41 compounds are common to both. The PERP values range more than 100,000-fold for exposures to different substances at the PEL. For some substances, exposures at the PEL would be close to the dose rate that produces tumors in 50% of test animals (*21*).

We have compared results for mutagens and nonmutagens using evaluations in Salmonella from the databases of the NTP and the U.S. Environmental Protection Agency Gene-Tox Program. Overall, mutagens are more often carcinogenic than nonmutagens; however, more than 40% of carcinogens tested in rats and mice are not mutagenic; 28% of noncarcinogens are mutagens that presumably are not acting as mutagens in rodents. Among carcinogens in rats or mice, a chemical positive in one species is more likely to be positive in the second species if it is a mutagen. Additionally, we examined the association between mutagenic response and administered dose level in positive rodent tests and found that more toxic carcinogens are significantly more likely to be mutagenic than less toxic carcinogens (*22*).

We have studied the proportion of chemicals that are positive among those reported in the CPDB for 10 different data sets: all chemicals, NCI/NTP chemicals, NCI chemicals reported before 1979, literature other than NCI/NTP, chemicals tested in both rats and mice (and among these, natural chemicals only and synthetic chemicals only), natural pesticides, mold toxins, and 22 chemicals in coffee. In each case, roughly half of the chemicals are positive according to the published author's opinion in at least one test (*14,22–25*). Among chemicals tested for mutagenicity as well as for carcinogenicity in both rats and mice, three-quarters are either mutagens or carcinogens. We have postulated that the administration of chemicals at the maximum tolerated dose (MTD) in standard animal cancer tests increases cell division (mitogenesis), which in turn increases rates of mutagenesis and thus carcinogenesis (*23,25–29*). A variety of studies on mechanism of carcinogenesis are consistent with this explanation (*23*). We conclude that at the low doses of most human exposures where cell killing does not occur, the hazards to humans of rodent carcinogens may be much lower than is commonly assumed.

The natural world makes up the vast bulk of chemical that humans consume each day in both weight and number. Since half of natural chemicals (as well as half the natural pesticides) are positive in animal tests, we conclude that our diet is filled with rodent carcinogens as defined by high-dose tests. The toxicological significance of exposures to synthetic chemicals has been examined in the context of exposures to naturally occuring chemicals, and we argue that animals have a broad array of inducible general defenses that at low-dose exposures are effective against both natural and synthetic toxins (*24,30*). The high proportion of positive results in cancer tests of both natural and synthetic chemicals and the similarity in their toxicology call into question the current efforts to protect public health by focusing regulatory action on synthetic chemicals.

The issue of extrapolating carcinogenesis results from one species to another has been addressed in two analyses of prediction between two closely related species, rats and mice. We have examined how well one can predict carcinogenicity from rats to mice and from mice to rats and discuss three factors that affect the accuracy of predicction: chemical class, mutagenicity, and the dose level at which a chemical is toxic. Additionally, we have described the frequency of a carcinogenic response in each target organ and have determined the predictive value of individual target sites in one species for carcinogenicity in the second species (*7,22*).

Overall for rats and mice, knowing that a chemical is positive in one of the species predicts positivity in the other species about 75% of the time. The overall predictive values between rats and mice provide some confidence in interspecies extrapolation; however, since a high proportion of test chemicals are positive by chance alone we would expect a positive predictive value between species of about 50% (*7,22*). Site-specific prediction between rats and mice is less accurate than overall prediction of positivity. Knowing that a chemical is positive at any site in one species gives about a 50% chance that it will be positive at the same site in the other species. Because many chemicals induce tumors at multiple sites, there is often more than one target site that is potentially a common site for the two species. Among the 101 chemicals with a site in common between rats and mice, for 45 chemicals the liver is the only site in common (*7*).

This work was supported through the University of California Berkeley by National Institute of Environmental Health Sciences Center grant ES01896 and through the Lawrence Berkeley Laboratory by contract DE-AC-03-76SF00098: Director, Office of Energy Research, Office of Health and Environmental Research, Division of U.S. Department of Energy, and by U.S. Environmental Protection Agency Agreement R-815619-01-0.

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